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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,643	10/31/2001	Bradley T. Hyman	19603/3541 (CRF D-2694A)	2817
7590 Michael L. Goldman NIXON PEABODY LLP Clinton Square P.O. Box 31051 Rochester, NY 14603			EXAMINER LAURITZEN, AMANDA L	
			ART UNIT 3737	PAPER NUMBER
			MAIL DATE 03/17/2009	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/001,643	Applicant(s) HYMAN ET AL.	
	Examiner Amanda L. Lauritzen	Art Unit 3737	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,8-14,16,18-21,24-30,32,34,36 and 38-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5,8-14,16,18-21,24-30,32,34,36 and 38-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02 January 2009 has been entered.

Rule 130, 131 or 132 Affidavit

Acknowledgement is made of the Affidavit submission of 02 January 2009 under 37 CFR 1.132. Remarks therein are effective to overcome the rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 under 35 U.S.C. 103(a) for obviousness over Turner et al. (US 6,329,531) in view of Hochman (US 2003/0236458).

Response to Arguments

Applicant's arguments with respect to Turner et al. (US 6,329,531) in view of Hochman (US 2003/0236458) have been fully considered and are persuasive. The rejection of claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 under 35 U.S.C. 103(a) over Turner et al. in view of Hochman has been withdrawn. Upon further consideration, new grounds of rejection are raised in view of Christie et al. (Abstract published in Society of Neuroscience Abstracts, 1998), of record. With respect to the steps that are purportedly missing in the prior art, applicant's declaration submitted 14 September 2004 makes clear that the missing steps are required in

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combination for the invention to function. Therefore, since the current independent claims do not recite all necessary steps (including using the particular wavelength required for multiphoton excitation, using the required power level and summing of the low energy photons) cited in that declaration as deficient in the prior art and essential to the invention, the current claims are incomplete and inoperable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, as being based upon a disclosure which is not enabling. The steps of using a thin skull, using the particular wavelength required for multiphoton excitation, using the required power level and summing of the low energy photons are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). As per applicant's admission in the declaration of 14 September 2004, in order for the invention to be enabled the following steps are required: using the particular wavelength required for multiphoton excitation, using the required power level and summing of the low energy photons. Therefore, these steps must be claimed.

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2. Claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Evidence that independent claims 1 and 19 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the reply filed 14 September 2004. The omitted steps are: using a particular wavelength required for multiphoton excitation, using the required power level, and summing of the low energy photons.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is inoperative and therefore lacks utility. The claimed subject matter does not claim the required steps for the invention to be operable. As per applicant's own submission in the declaration filed 14 September 2004, in order for the invention to be operable the following steps are required: using a particular wavelength required for multiphoton excitation, using the required power level, and summing of the low energy photons.

2. Claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. In order for a process to be patentable under 35 U.S.C. 101, it must be tied to another statutory class (such as a particular apparatus), or transform underlying subject matter (such as an article or materials) to a different state or thing. The claim(s) must positively recite the thing or product to which the

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process is tied, for example, by identifying the apparatus that accomplishes the method steps, or positively recite the subject matter that is being transformed, for example, by identifying the material that is being changed to a different state (see *In re Bilski*, 545 F.3d 943, 88 USPQ2d 1385, Fed. Cir. 2008). In the instant case, the method is directed to activating brain tissue of a mammal by application of radiation, but the source of the radiation is not claimed in the independent claims, for example, a particular laser or other energy source.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. Claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gervais et al. (US 2002/0115717) in view of Alfano et al. (US 6,280,386) and Christie et al. (Abstract published in Society of Neuroscience Abstracts, 1998).

Gervais et al. teach a method of detecting a neurodegenerative disease in vivo by observing the fluorescence of amyloid plaques and/or neurofibrillary tangles in a mammal by activating the tissue of interest, including the brain, in vivo and by using optical imaging in the infrared range under conditions effective to promote a fluorescence characteristic in order to diagnose amyloidosis related to diseases such as early-stage Alzheimer's (see pars. 9-12, 35 and 156 describing detecting fluorescence with a photoactive agent to optically image the brain in order to diagnose disease conditions for cases such as Alzheimer's).

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While Gervais et al. do not explicitly teach comparing the fluorescence characteristic to a standard fluorescence emitted by exciting healthy brain tissue of the mammal under the same conditions used to carry out the activating, it is well within the knowledge of skilled artisans that there must be some comparison to a standard in order to determine the significance of what is being identified in the image. For example, if there is a luminous site in the image, either comparison with a normal image or some other type of normalization will be undertaken to ensure that what is being observed is of significance. Such image processing is described by Alfano et al., in col. 6, lines 17-52, wherein subtraction between images and normalization is undertaken in order to obtain a better image and thereby allow diagnosis of disease.

Photo-activation by laser and pulsed radiation are well known imaging expedients to skilled artisans. Gervais et al. in view of Alfano et al. do not explicitly teach multiphoton excitation to detect neurodegenerative diseases; however, in the same field of endeavor, Christie et al. (Society of Neuroscience Abstracts, 1998) teach multiphoton excitation to detect neurodegenerative diseases such as Alzheimer's to enhance the ability to image amyloids deep within living tissues using fluorophores. It would have been obvious to one of ordinary skill in the art at the time of invention to modify Gervais et al. in view of Alfano et al. to incorporate the teachings of Christie et al. to make use of multiphoton excitation as it improves visualization of amyloid plaques deep within tissue.

With respect to a thin skull, it would have been necessary to thin the skull in the case of multiphoton excitation as taught by Christie et al. since the abstract refers to gathering information from brain tissue, and it is necessary to remove intervening bone structure in order to gather data.

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2. Claims 1-5, 8-14, 16, 18-21, 24-30, 32, 34, 36 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (US 6,329,531) in view of Hochman (US 2003/0236458) and Christie et al. (Abstract published in Society of Neuroscience Abstracts, 1998).

Turner et al. disclose a method for detecting a neurodegenerative disease comprising activating brain tissue by application of radiation under conditions to promote excitation of the brain tissue and to emit a fluorescence characteristic with administration of a photoactive compound (refer to the Abstract in which the disease diagnosis is Alzheimer's by applying radiation with wavelength in the visible to NIR region for detection of amyloid plaques in the brain). The photoactive compounds disclosed by Turner et al bind to the A-beta plaques (col. 2, lines 58-64). In-vivo detection of amyloid plaques is characterized as having a laser-induced fluorescence characteristic differing from that in normal tissue and is disclosed to produce an image (col. 2, line 65 – col. 3, line 2; also col. 16, lines 47-52 for applying laser light with wavelength of 740nm). The method of Turner also specifies identification of neurofibrillary tangles (col. 1, line 21).

Turner et al. disclose all features of the invention as substantially claimed but do not specifically address the specifics of the pulsed radiation, carrying out the procedure on a skull that has been thinned or opened, or comparison to a standard fluorescence for making diagnosis. In the same field of endeavor, Hochman discloses diagnosing neurological disorders with an "invasive or semi-invasive" procedure that is understood to include removal of a portion of the skull and/or thinning of the skull to enable access to the brain (par. 42). Additionally, Hochman describes optical sources providing either continuous or non-continuous (i.e., pulsed)

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illumination (par. 41; also par. 146). Hochman discloses comparing patient data to a control and/or standard data set for the purpose of diagnosis and also acquires fluorescence naturally characteristic to the tissue without administering a contrast agent (i.e., autofluorescence) at par. 45. Hochman further discloses application of energy with a wavelength of about 800nm to analyze deeper areas of tissue (par. 144). It would have been obvious to one of ordinary skill in the art at the time of invention to have modified the method of Turner to include comparison to a standard data set in order to make a diagnosis (as taught by Hochman at par. 45) with removal of impeding bone structure or thinning of the skull as is implied under the invasive brain procedure of Hochman (par. 42) to enable access to the tissue of interest. It would have been obvious to one of ordinary skill in the art at the time of invention to have provide a pulse width in the femtosecond range with a mode-locked laser in order to concentrate power delivered over a very short time period.

Turner et al. in view of Hochman do not explicitly teach multiphoton excitation in detection of the plaques characteristic to neurodegenerative diseases; however, in the same field of endeavor, Christie et al. (Society of Neuroscience Abstracts, 1998) teach multiphoton excitation to detect neurodegenerative diseases such as Alzheimer's to enhance the ability to image amyloids deep within living tissues using fluorophores. It would have been obvious to one of ordinary skill in the art at the time of invention to modify Turner et al. in view of Hochman to incorporate the teachings of Christie et al. to make use of multiphoton excitation as it is disclosed to improve visualization of amyloid plaques deep within tissue.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda L. Lauritzen whose telephone number is (571)272-4303. The examiner can normally be reached on Monday - Friday, 8:30am - 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian L. Casler can be reached on (571) 272-4956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amanda L. Lauritzen/
Examiner, Art Unit 3737

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